**High-Sensitivity Cardiac Troponin and the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guidelines for the Evaluation and Diagnosis of Acute Chest Pain**

Yader Sandoval1 MD, Fred S. Apple2 PhD, Simon A. Mahler3 MD, Richard Body4 MB ChB, Paul O. Collinson5 MB BChir, MD, and Allan S. Jaffe1,6 MD on behalf of the IFCC Committee7 on the Clinical Application of Cardiac Biomarkers (IFCC-CB).

1. Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA
2. Departments of Laboratory Medicine and Pathology, Hennepin Healthcare/Hennepin County Medical Center and University of Minnesota, Minneapolis, MN, USA.
3. Department of Emergency Medicine, Wake Forest School of Medicine, Winston Salem, NC, USA.
4. Emergency Department, Manchester University NSH Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; Division of Cardiovascular Sciences, The University of Manchester, Manchester, UK; Healthcare Sciences Department, Manchester Metropolitan University, Manchester, UK.
5. Department of Clinical Blood Sciences and Cardiology, St. George’s University Hospitals NHS Foundation Trust and St. George’s University of London, United Kingdom.
6. Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
7. Members and consultants on the International Federation of Clinical Chemistry and Laboratory Medicine Committee on Clinical Applications of Cardiac Bio-Markers (IFCC C-CB) are Fred S. Apple Ph.D, Chair, Allan S. Jaffe, M.D. Jorge Ordoñez Llanos, MD, PhD, Paul O. Collinson MB BChir, MD, Richard Body MB ChB, MRCSEd, FRCEM, PhD, Amy K. Saenger Ph.D., Peter A. Kavsak, Ph.D. Torbjørn Omland, MD, MPH, PhD,, Kristin Moberg Aakre, MD, PhD, Ola. Hammarsten M.D.

Manuscript word count: 3841. References: 90

Abstract words - 220

Tables and figures: 5

**CORRESPONDING AUTHOR**

Allan S. Jaffe, M.D.

Department of Cardiovascular Diseases and Department of Laboratory Medicine and Pathology.

Mayo Clinic, Gonda 468, 200 1st, SW, Rochester, MN, 55905.

Email: [jaffe.allan@mayo.edu](mailto:jaffe.allan@mayo.edu).

Telephone: 507284-1648. Fax: 507-266-0228

**DISCLOSURES**

**Dr. Sandoval** has previously participated in advisory boards for Abbott Diagnostics and Roche Diagnostics, and has also been a speaker for Abbott Diagnostics; all without personal financial compensation.

**Dr. Apple** is an Associate Editor for Clinical Chemistry; Consultant: HyTest; Advisory Boards: Werfen, Siemens Healthineers, Qorvo Biotechnologies; PI on Industry Funded Grants (non-salaried) on cardiac biomarkers through Hennepin Healthcare Research Institute: Abbott Diagnostics, Abbott POC, BD, Beckman Coulter, Ortho-Clinical Diagnostics, Roche Diagnostics, Siemens Healthcare (Healthineers), ET Healthcare, Quidel.

**Dr. Mahler** receives research support from Roche Diagnostics, Abbott Laboratories, Ortho Clinical Diagnostics, Siemens, Grifols, Pathfast, Quidel, Genetesis, Cytovale, and HRSA (1H2ARH399760100). He is a consultant for Roche, Quidel, Abbott, Genetesis, Inflammatix, and Amgen and the Chief Medical Officer for Impathiq Inc.

**Dr. Body** has received research grants from Roche, Abbott Point of Care and Siemens Healthineers, and has consulted or is consulting for Roche, Siemens, Abbott, Beckman Coulter, Radiometer, LumiraDx, Creavo and Aptamer Group.

**Dr. Collinson** is anAssociate Editor of the Journal of Laboratory Medicine. Advisory Boards: Radiometer, Psyros Diagnostics.

**Dr. Jaffe** has consulted or is presently consulting for most of the major diagnostic companies, including Beckman, Abbott, Siemens, ET Healthcare, Roche, Ortho Diagnostics, Radiometer, RCE technologies, Astellas and Sphingotec. He also consults for Amgen and Novartis.

**KEYWORDS**

1. Chest pain
2. High-sensitivity cardiac troponin
3. Acute myocardial infarction
4. Myocardial injury
5. Clinical practice guidelines

**ABBREVIATIONS**

1. hs-cTn: high-sensitivity cardiac troponin
2. IFCC: International Federation of Clinical Chemistry and Laboratory Medicine
3. AHA: American Heart Association
4. ACC: American College of Cardiology
5. URL: upper-reference limit
6. CDP: clinical decision pathway
7. RCT: randomized clinical trials
8. ESC: European Society of Cardiology
9. FDA: Food and Drug Administration
10. ED: emergency department

**ABSTRACT**

The 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guidelinesfor the evaluation and diagnosis of acute chest pain make important recommendations that include the recognition of high-sensitivity cardiac troponin (hs-cTn) as the preferred biomarker, endorsement of 99th percentile upper-reference limits (URL) to define myocardial injury, and the use of clinical decision pathways (CDPs), as well as acknowledgement of the uniqueness of women and other special patient subsets. Details, however, on how to integrate hs-cTn into clinical practice are less extensively addressed. Clinicians should be aware of some of the analytical aspects related to hs-cTn assays regarding the limit of detection (LoD) and the limit of quantitation (LoQ), and how they are used clinically, especially for the single sample strategy to rule-out acute myocardial infarction. Likewise, it is important for clinicians to understand issues related to the derivation of the 99th percentile upper-reference limit (URL), the value of sex specific 99th percentile URLs, how to use changing concentrations (deltas) to facilitate diagnosis and risk-stratification of patients with suspected acute coronary syndrome, including the differentiation of acute from chronic myocardial injury, and how to best integrate the use of hs-cTn with CDPs. Finally, with the use of hs-cTn, conditions such as type 2 myocardial infarction become more common, whereas others such as unstable angina become less frequent but still occur. Sections relating to these issues are included.

**INTRODUCTION**

The present document is an evidence-based, multidisciplinary, critical appraisal of the acute chest pain and high-sensitivity cardiac troponin (hs-cTn) recommendations from the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guidelines1 for the evaluation and diagnosis of chest pain. It is endorsed by the International Federation of Clinical Chemistry and Laboratory Medicine Committee on Clinical Applications of Cardiac Bio-Markers (IFCC C-CB). Our appraisal involves laboratorians, emergency physicians, as well as non-invasive and interventional cardiologists. The recently published AHA/ACC guidelines1 make important recommendations that include the recognition of hs-cTn as the preferred biomarker, endorsement of 99th percentile upper-reference limits (URL) to define myocardial injury, the use of clinical decision pathways (CDPs), as well acknowledgement of the uniqueness of women and other special patient subsets. However, additional detail about how to integrate hs-cTn into clinical practice to assist with triage, diagnosis, and risk-stratification of patients with suspected acute coronary syndrome (ACS) would be helpful. The goal of this IFCC C-CB endorsed appraisal is to provide additional, constructive, evidence-based educational recommendations pertaining to cTn that should be considered for integration into the guidelines and into clinical practice.

**BACKGROUND**

hs-cTn assays have been used clinically outside the United States (US) for more than a decade. Data supporting their use have evolved from observational studies to randomized clinical trials (RCT)2-5. European Society of Cardiology (ESC) guidelines6-8 have provided class I recommendations for hs-cTn since 2011 (**Table 1**). The 2020 ESC guidelines8 recommend 0/1 hour (h) and 0/2h early rule out algorithms with class IB recommendations. In contrast to the AHA/ACC guidelines1, the ESC8 recommendations provide assay-specific risk stratification concentration thresholds that are helpful to clinicians (Figure 1).

Multiple hs-cTn assays have received 510k clearance by the Food and Drug Administration (FDA) for clinical use in the US since 20179. The characteristics of all cTn assays are tabulated and updated every 4 months by the IFCC C-CB10. There are a paucity of US guidelines about how to incorporate cTn assays into clinical practice. This is an important gap given the broad clinical useof cTn testing11, 12 in the US and the lower incidence of myocardial infarction in the UScompared with European studies13-15. This difference means that some of the thresholds that are derived from selected chest pain cohorts from Europe may not be as applicable in the all-comer, heterogeneous patient populations presenting to US emergency departments (ED). While the AHA/ACC guidelines reference data largely derived from European chest pain studies, there are an increasing number of US hs-cTn based studies13-24 that have evaluated these approaches as well.

The ACC/AHA guidelines1 provide a class I recommendation to measure cTn in patients with chest pain, and preferably to use hs-cTn assays. Opportunities exist, however, to educate clinicians more extensively about the analytics of hs-cTn assays25-28, many of which are important to understand how to best implement their use in clinical practice. The efficient assessment of patients with chest pain with hs-cTn assays requires the development and maintenance of evidence-based rapid risk-stratification protocols for acute myocardial infarction, standardized sample collection processes with acceptable turnaround times that allow for rapid rule-in and rule-out algorithms, consistent reporting in electronic health records, and laboratory analytical quality control processes to ensure that hs-cTn results are reliable for decision-making25. The evaluation of patients with suspected ACS should integrate all aspects of these multiple processes and represent a multi-disciplinary effort that involves partnership with laboratory medicine with clinicians from emergency medicine, internal or family medicine, and cardiology.

To provide a comprehensive education to clinicians, we have addressed the evidence-based literature, including several guidelines and expert consensus documents from professional organizations29, 30 (**Table 2**), as well as guidance papers from individual centers about how to use hs-cTn for the evaluation of patients with chest discomfort. We acknowledge that some of the information cited has been published after the guidelines1 were finished. We will include some of those selected manuscripts when they provide important insights related to hs-cTn assays. When we discuss these data, we will acknowledge that these references were published after completion of the guidelines.

**AN EVIDENCE-BASED APPRAISAL OF THE GUIDELINES RELATED TO THE USE OF HIGH SENSIVITY CARDIAC TROPONIN**

***Analytical issues***

The AHA/ACC guidelines recognize hs-cTn as the preferred biomarker for the detection of myocardial injury and endorse the assay-specific overall 99th percentile URL1. It should be noted that concentrations should be reported in ng/L units and concentrations rounded to whole numbers without decimals to avoid reporting or interpretation errors25-27. Using ng/L differentiates assays as ‘high sensitivity’ from contemporary assays.

***The 99th percentile upper-reference limit***

The new ACC/AHA guidelines1, as well as all other major guidelines8, 31 including the Universal Definition32 of Myocardial Infarction (UDMI) recommend the 99th percentile URL as the threshold for myocardial injury and in the proper clinical setting to support the diagnosis of myocardial infarction. However, there are some important issues for clinicians to be aware. It is important to understand how these thresholds are derived as they influence the sensitivity with which myocardial injury is detected33, 34. The most recent (2022) IFCC and American Association of Clinical Chemistry (AACC) guidelines recommend that the 99th percentile URL be derived from a sample size of at least 400 male and 400 female “healthy” individuals that should be screened with the use of questionnaires to allow for exclusion of those with cardiovascular comorbidities and those on cardiovascular medications, as well as the use of biomarkers such as NT-proBNP, hemoglobin A1C, and eGFR to exclude those with subclinical disease25. Using rigorous selection criteria to define normality will result in lower 99th percentiles, whereas using less stringent criteria will result in higher 99th percentiles. Multiple studies demonstrate that the 99th percentile thresholds can vary significantly based on the cohort selection35-37. If one is not cautious about the thresholds used, it can make comparisons between assays problematic35, 38. Support by the guidelines for a consistent approach in this area would have helped the standardization of the 99th percentile URL.

In addition, despite the fact that all major guidelines and the UDMI recommend use of the 99th percentile URL8, 31, 32, many medical centers still do not use this threshold39-42. Not only does this make the diagnosis of myocardial infarction inconsistent with any given assay, but it also limits the applicability of recommended approaches in guidelines that are based on the 99th percentile. All novel risk-stratification approaches using hs-cTn assays have been validated based on the gold standard suggested by the UDMI32, which includes the appropriate 99th percentile URLs34. Thus, opportunities exist to continue to educate clinicians about the importance of using the 99th percentile as an important criterion to standardize the diagnosis of myocardial infarction for clinical, research, and regulatory purposes34. Sensitizing clinicians to the importance of this issue on the part of the guidelines would facilitate the standardization of the 99th percentile to support the diagnosis of acute MI.

Although the 2021 AHA/ACC guidelines1 acknowledge and recommend that clinicians be “*familiar with the analytical performance and the 99th percentile upper reference limit that defines myocardial injury for the cTn assay used at their institution*” as a class I recommendation (LOE – CEO), the clinical decision pathway table (Table 6 in the guidelines) reports hs-cTnT concentration thresholds that are not applicable for all assays given cTn assays are not standardized. Given 99th percentile URLs are assay-specific, this area is one where clinicians would be well advised to use caution.

***Sex-specific 99th percentile upper-reference limits* (figure 2)**

Class IB recommendations (LOE-B-NR)1 are made that “*women who present with chest pain are at risk for underdiagnosis, and potential cardiac causes should always be considered*”. The guidelines acknowledge sex-specific hs-cTn URLs1, 43,but do not elaborate further or advocate their use. There are extensive data35-37 documenting that women have lower 99th percentiles than men. That is why the Fourth UDMI32, as well as several guideline groups25 endorse sex-specific 99th percentiles for clinical practice.. All FDA-cleared hs-cTn assays report sex-specific 99th percentiles10 (**Table 3**). Clinically, hs-cTnI and hs-cTnT sex-specific 99th percentiles improve the underdiagnosis of women14, 43. The debate about their impact on outcomes is the focus of an ongoing RCT (CODE-MI, hs-cTn Optimizing the Diagnosis of Acute Myocardial Infarction/Injury in Women) (NCT03819894)44. If robust race-specific data become available, as has occurred with sex-specific data, they too would be relevant for consideration.

***Single-sample rule-out of acute myocardial infarction using hs-cTnI and hs-cTnT assays***

Among patients who are not early presenters (symptom onset >2 hours), extensive data exist to support the use a single low hs-cTn measurement to identify patients with a low risk for acute myocardial infarction3-5, 16, 17, 19, 45-47. These patients have been shown to be unlikely to suffer major adverse cardiovascular events during short- and long-term follow-up45, 48. It is a valuable strategy for clinicians to understand and use as it can reduce hospital overcrowding and facilitate the early discharge of selected low-risk patients. A “very low” hs-cTn concentration often refers to either an analytical threshold such as the limit of detection (LoD) or limit of quantitation (LoQ) or may refer to a validated hs-cTn concentration that is higher than the LoD or LoQ that is optimized to maximize the proportion of eligible low-risk patients while maintaining safety. The guidelines1 recommendations are focused on the LoD analytical threshold. However, despite extensive validation of the approach, the 2021 AHA/ACC guidelines1 provide only a class 2a recommendation (LOE-NR) that “*for patients with acute chest pain, a normal electrocardiogram (ECG), and symptoms suggestive of ACS that began at least 3 hours before ED arrival, a single hs-cTn concentration that is below the limit of detection on initial measurement (time zero) is reasonable to exclude myocardial injury*”. Based on their recommendation to use of the LoD for hs-cTn assays and the large number of available studies including meta-analyses45-47, randomized trials3, 4, and US based cohort trials16, 19, a higher recommendation than class 2a (level of evidence B – nonrandomized) would have been appropriate.

A critically important educational caveat, however, is the fact that none of the hs-cTn assays cleared by the FDA are allowed to report to the LoD9, 49. hs-cTn assays are only FDA-cleared to report to the LoQ; the lowest concentration with a 20% CV (coefficient of variation)28, 49, 50. The LoQ concentration threshold is invariably above the LoD, although some companiess by reporting ranges from across their studies and/or rounding up to whole numbers, can give the false impression that the LoD and LoQ are the same10, 51. Although the difference between the LoD and LoQ can be small for some assays, the thresholds are unequivocally distinct in their definition51 (**Figure 3**), imprecision standards, concentrations10 (**Table 3**), and evidence-base support for their clinical use. Therefore, at present the AHA/ACC recommendation to use the LoD is not clinically applicable in the US. There are some data17, 18, 20, 52, 53 indicating that use the LoQ is safe for this purpose.

Finally, we emphasize that there are robust clinical data for some hs-cTn assayssuggesting that hs-cTn concentrations well above both the LoD and LoQ are of value in ruling-out myocardial infarction5, 16, 19, 45, 54. For example, the High-STEACS rule-out pathway43, 45, 55, which evaluated an optimized concentration of <5 ng/L to exclude myocardial infarction with the Abbott hs-cTnI assay, was validated for safety and efficacy in the HiSTORIC (31,492 patients) trial5,. which was published after the guidelines were completed. The study showed an adverse event rate of only a 0.3% (56/ 16 792) (myocardial infarction or cardiac death) at 30-days5. There were validation studies before HiSTORIC, including the US ‘UTROPIA’ cohort data19, and a meta-analysis45 of 22,457 patients across 19 cohorts to support this approach. This approach is also, applicable using other hs-cTnI assays16. This is an approach that might well be worth considering when/if centers are using hs-cTn assays with the appropriate evidence-base to support implementation. Recent data soon to be published in Circulation confirm the safety of the use of a value at the LOQ (<6ng/L) for the single sample rule out using hscTnT56. Point of care assays may soon to here to further facilitate this important approach.

***Information about a changing pattern of values (deltas)***

Conceptually, it would have been educational to provide some guidance regarding the changing pattern (deltas) of cTn values since this element is critical when serial measurements are used27,57 These considerations are complex and assay-dependent, but some principles have been published by the biomarker group of the Acute Cardiovascular Care Association57 and by the IFCC-CB27. Validated assay-specific deltas for low and high-risk as recommended by the ESC guidelines8 are worth considering in the US, assuming centers use the appropriate 99th percentile URLs that the data are based upon.

There also are important concepts that underly the use of changing patterns (Figure 4). For patients without myocardial injury, the absence of significant cTn concentration changes over time identifies lower-risk patients58. Conversely, the presence of changes identifies higher-risk patients and improves diagnostic specificity15,59. Even with the use of delta changes, the positive predictive value (PPV) and specificity for myocardial infarction are far from perfect15,59. Clinicians need to be aware that these change criteria define acute myocardial injury, which can occur for many reasons other than myocardial infarction32. The increase in specificity and PPV necessary to diagnose myocardial infarction must come from other clinical data such as the history, ECG and/or imaging. For patients without cTn increases above the 99th percentile at baseline or only modest increases, absolute concentration deltas are superior to relative (%) changes, 57,60. Among patients with chronic increases >99th percentile, the absence of significant changes (in this instance a percentage change <20% delta) is indicative of chronic myocardial injury in the appropriate clinical context 32. Because hs-cTn assays detect more chronic myocardial injury61 the importance of differentiating between acute and chronic injury with serial sampling should be emphasized32.

The Fourth UDMI32 suggests that rising and falling patterns have similar importance but reflect different timing, however definitive evidence is needed. In the interim, the approach suggested in the UDMI is a reasonable for clinicians to follow. While hs-cTn assays measure very low cTn concentrations and detect changes (deltas) with higher precision than contemporary assays (which are being phased out by manufacturers), some have been concerned that very small deltas may not be detected with adequate precision62-64 which leads to the potential for patient misclassification.

**Single sample hs-cTn for identification of high-risk patients based on higher concentrations**

Increased baseline cTn concentrations >99th percentile are specific for myocardial injury32 and identify high-risk patients. Higher concentrations such as those endorsed by the ESC help identify even higher risk patients8,65. However, with the broader use of hs-cTn testing in the US, clinicians need to be aware that while specific for myocardial injury these approaches may lack specificity for myocardial infarction especially in elderly patients, those with critical illness, and those with end stage renal disease66,67. In these situations, assessing changes over serial measurements (deltas) become even more important to improve diagnostic specificity15,27,57,58.

**Clinical decision pathways and risk-stratification groups**

One of the benefits of hs-cTn assays is that they expedite the evaluation of patients with suspected ACS3, 5, predominantly because of the early identification of low-risk patients eligible for early discharge. This reduces ED overcrowding without increasing resource utilization14, 23. The AHA/ACC recommendations1 for the intermediate group may do the opposite, unless hs-cTn results are considered. CDP and risk scores are used by ED physicians to evaluate undifferentiated patients. There are guidelines that suggest how to integrate them with hs-cTn assays29, 30. The ACEP recommends the HEART and TIMI scores to predict the rate of 30-day major adverse cardiovascular event (MACE)29. The ACEP policy29 suggests patients are eligible for accelerated discharge when they are low-risk for 30-day MACE based on 1) a non-ischemic electrocardiogram, and 2) “negative” serial hs-cTn results at presentation and 2h. The SAEM guidelines30 which focuses on recurrent, low-risk chest pain; i.e., those with a HEART score <4 also provide similar guidelines.

***Integration of hs-cTn with risk scores for the intermediate risk group***

They 2021 AHA/ACC guidelines1 provide a class 1B recommendation (LOE-B-NR) that “*in patients presenting with acute chest pain and suspected ACS, clinical decision pathways (CDPs) should categorize patients into low, intermediate, and high-risk strata to facilitate disposition and subsequent diagnostic evaluation*”. While the low-risk group is well defined, the definitions for intermediate and high-risk groups are less definitive. One could be designated at intermediate risk based on a risk score alone even with hs-cTn concentrations below the 99th percentile. However, in most situations, the presence or absence of myocardial injury based on cTn concentrations above or below the 99th percentile is a key element that predicts adverse events32. Thus, should patients with an intermediate risk score (e.g. HEART score of 4-6) without myocardial injury have the same risk profile and care recommendations as a patient with increased cTn concentrations above the 99th percentile? We would suggest these groups are likely different, and that patients with increased cTn above the 99th percentile URL indicative of myocardial injury are likely at different risk depending on whether the changes are acute or chronic60,67,68, and their magnitude64,70.

Since there are multiple ways to be designated intermediate risk, should the class I

recommendations for transthoracic echocardiography, coronary computed tomography angiography

and stress testing be applied to all intermediate patients irrespective of their hs-cTn results? To the best of our knowledge, there are no strong data for those without myocardial injury. Noninvasive evaluations in those with elevated risk scores but non-ischemic ECGs and non-elevated cTn concentrations <99th percentile URL have a low diagnostic yield without evidence for improved clinical outcomes71-74. This potential for over testing could exacerbate ED and hospital overcrowding and increase length of stay. In addition, it is unclear whether all or only some subset of those at intermediate risk should be admitted to observation units. The guidelines state with a 2a recommendation (LOE-A) “*for intermediate-risk patients with acute chest pain, management in an observation unit is reasonable to shorten length of stay and lower cost relative to an inpatient admission”1.* In a large multisite studyof ED patientswithout an initial diagnosis of myocardial infarction, there appeared to be no benefit in 30-day outcomes associated with observation or hospital admission75. Another large multisite study of ED patientswithout an initial diagnosis of myocardial infarction found wide variation in physicians’ admission rates and no improvement in patient outcomes related to higher admission rates76. Our concern is that patients without myocardial injury, even if “intermediate’ risk based on a risk scores, do not necessarily require additional evaluations either in an observation unit or the hospital. There may be some patients who need evaluation in the outpatient setting.

**Integration of hs-cTn with risk scores for the high-risk group**

The guidelines1 provide a class I recommendation (LOE-C-EO) for “*patients with acute chest pain and suspected ACS who are designated as high risk, invasive coronary angiography is recommended.”*  Our concern is that this recommendation includes those with increased risk scores based on age and comorbidities without myocardial injury. Studies suggest that for patients with ACS and hs-cTn concentrations below the 99th percentile there is no benefit from a *routine* invasive approach77.

**Discordance with ESC guidelines**

There is discordance between the 2020 ESC8 and the 2021 AHA/ACC1 guidelines. The ESC guidelines8 provide class I recommendations for the 0/1h and 0/2h algorithms. They have downgraded the 0/3h algorithm based on multiple studies46,78,81 demonstrating a reduced ability to exclude myocardial infarction. The latter likely occurs because of an improved rule-out performance when incorporating the “single sample rule out”, which is advocated in the 0/1h and 0/2h algorithms but not the 0/3h algorithm7, 8. The AHA/ACC guidelines do not make this distinction when tabulating the available hs-cTn protocols, but it is important to acknowledge that the 0/3h algorithm has been downgraded because of the data46,78,81  showing it is not as safe as the 0/1h and 0/2h algorithms.

**OTHER GAPS**

***Definition of MACE and acceptable miss rates***

Defining what constitutes an acceptable “miss rates” is critical. Previous surveys82 have suggested that the accepted miss rate for ED physicians is 1%. The 2018 ACEP policy29 indicated that “*any discussion of accuracy in ED testing for potential NSTEMI needs to include discussion of acceptable rate of missed diagnosis*” and recommended a miss rate of 1% to 2% for 30-day MACE. They defined MACE as Q-wave MI, non-Q-wave MI (NSTEMI), death, or target lesion revascularization within 30-days following the ED evaluation29. The inclusion of revascularization following an ED presentation was controversial as an endpoint since it may not reflect information from the clinical presentation but be related in some cases more to information derived during the evaluation itself. The 2021 AHA/ACC chest pain guidelines1 indicate that patients with a 30-day risk of death or MACE <1% should be potentially designated as “low-risk” but do not indicate what constitutes MACE, which would have been informative.

***Requiem for unstable angina: not yet***

While unstable angina is less frequent using hs-cTn assays, the entity has not yet disappeared83-85. Education on this fact would be helpful because it alerts clinicians that although hs-cTn assays are excellent in ruling out acute myocardial infarction, unstable angina presentations and severe stable obstructive coronary artery disease (CAD) still occur 84,855. We would hasten to add however that the presence of CAD alone in the age of widespread use of CCTA is insufficient to diagnose unstable angina in the absence of appropriate symptoms. Some caution is necessary in this area. There are good data that patients benefit from an invasive strategy when they have an increased cTn value.8 In some studies, however, they do not benefit when the cTn is not increased 86,87 and in some studies, there have even been claims of detriment77,88.

***Type 2 myocardial infarction is common***

With hs-cTn assays, the major increase in myocardial infarction diagnoses is largely due to type 2 events 89,90. In the US, some of the data indicate there may be more type 214, 24 than type 1 myocardial infarctions. In the absence of robust data and heterogeneity intrinsic to this patient population, expert recommendations are to focus on treating the underlying supply-demand imbalances/triggers. For selected patients, such as those with microvascular disease and/or epicardial vasospasm, SCAD (spontaneous coronary artery dissection), or coronary embolus angiography is needed90.

***cTn sampling in relation to symptom onset***

Rapid hs-cTn algorithms can fail in patients that present early54 (<2-3h) as in those that present late (>12 hours although there is no consensus). It may take time for cTn signals to develop in the patients who present early, and more time and additional samples to observe a declining pattern indicative of an acute event in those who present late (**Figure 5**). Both cautions are included in the UDMI32.

**CONCLUSION**

We have provided evidence-based perspectives to assist with the evaluation of patients with suspected ACS and the proper use of hs-cTn assays to integrate them into the recent ACC/AHA guidelines. It is encouraging and a good start to see hs-cTn incorporated into new guidelines. Ideally their use should be coordinated globally across all medical disciplines. Opportunities exist to address many key elements that we have articulated. Perhaps they can be addressed in upcoming policy documents from the major societies.

**REFERENCES**

1. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, Diercks DB, Gentile F, Greenwood JP, Hess EP, Hollenberg SM, Jaber WA, Jneid H, Joglar JA, Morrow DA, O'Connor RE, Ross MA and Shaw LJ. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144:e368-e454.

2. Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, Sandeman D, Stables CL, Adamson PD, Andrews JPM, Anwar MS, Hung J, Moss AJ, O'Brien R, Berry C, Findlay I, Walker S, Cruickshank A, Reid A, Gray A, Collinson PO, Apple FS, McAllister DA, Maguire D, Fox KAA, Newby DE, Tuck C, Harkess R, Parker RA, Keerie C, Weir CJ and Mills NL. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet*. 2018;392:919-928.

3. Chew DP, Lambrakis K, Blyth A, Seshadri A, Edmonds MJR, Briffa T, Cullen LA, Quinn S, Karnon J, Chuang A, Nelson AJ, Wright D, Horsfall M, Morton E, French JK and Papendick C. A Randomized Trial of a 1-Hour Troponin T Protocol in Suspected Acute Coronary Syndromes: The Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T Study (RAPID-TnT). *Circulation*. 2019;140:1543-1556.

4. Carlton EW, Ingram J, Taylor H, Glynn J, Kandiyali R, Campbell S, Beasant L, Aziz S, Beresford P, Kendall J, Reuben A, Smith JE, Chapman R, Creanor S and Benger JR. Limit of detection of troponin discharge strategy versus usual care: randomised controlled trial. *Heart*. 2020;106:1586-1594.

5. Anand A, Lee KK, Chapman AR, Ferry AV, Adamson PD, Strachan FE, Berry C, Findlay I, Cruikshank A, Reid A, Collinson PO, Apple FS, McAllister DA, Maguire D, Fox KAA, Newby DE, Tuck C, Harkess R, Keerie C, Weir CJ, Parker RA, Gray A, Shah ASV and Mills NL. High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction: A Stepped-Wedge Cluster Randomized Controlled Trial. *Circulation*. 2021;143:2214-2224.

6. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W and Zahger D. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999-3054.

7. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF and Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267-315.

8. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D and Siontis GCM. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289-1367.

9. Apple FS, Fantz CR and Collinson PO. Implementation of High-Sensitivity and Point-of-Care Cardiac Troponin Assays into Practice: Some Different Thoughts. *Clin Chem*. 2021;67:70-78.

10. International Federation of Clinical Chemistry and Laboratory Medicine Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) (Tables v092021 accessed November 18th, 2021): .

11. Makam AN and Nguyen OK. Use of cardiac biomarker testing in the emergency department. *JAMA Intern Med*. 2015;175:67-75.

12. Shah ASV, Sandoval Y, Noaman A, Sexter A, Vaswani A, Smith SW, Gibbins M, Griffiths M, Chapman AR, Strachan FE, Anand A, Denvir MA, Adamson PD, D'Souza MS, Gray AJ, McAllister DA, Newby DE, Apple FS and Mills NL. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study. *Bmj*. 2017;359:j4788.

13. Vigen R, Kutscher P, Fernandez F, Yu A, Bertulfo B, Hashim IA, Molberg K, Diercks DB, Metzger JC, Soto J, Alzubaidy D, Thibodeaux L, Joglar JA, de Lemos JA and Das SR. Evaluation of a Novel Rule-Out Myocardial Infarction Protocol Incorporating High-Sensitivity Troponin T in a US Hospital. *Circulation*. 2018;138:2061-2063.

14. Ola O, Akula A, De Michieli L, Dworak M, Crockford E, Lobo R, Rastas N, Knott JD, Mehta RA, Hodge DO, Grube E, Karturi S, Wohlrab S, Tak T, Cagin C, Gulati R, Jaffe AS and Sandoval Y. Clinical Impact of High-Sensitivity Cardiac Troponin T Implementation in the Community. *J Am Coll Cardiol*. 2021;77:3160-3170.

15. Sandoval Y, Smith SW, Thordsen SE, Bruen CA, Carlson MD, Dodd KW, Driver BE, Jacoby K, Johnson BK, Love SA, Moore JC, Sexter A, Schulz K, Scott NL, Nicholson J and Apple FS. Diagnostic Performance of High Sensitivity Compared with Contemporary Cardiac Troponin I for the Diagnosis of Acute Myocardial Infarction. *Clin Chem*. 2017;63:1594-1604.

16. Sandoval Y, Nowak R, deFilippi CR, Christenson RH, Peacock WF, McCord J, Limkakeng AT, Sexter A and Apple FS. Myocardial Infarction Risk Stratification With a Single Measurement of High-Sensitivity Troponin I. *J Am Coll Cardiol*. 2019;74:271-282.

17. Allen BR, Christenson RH, Cohen SA, Nowak R, Wilkerson RG, Mumma B, Madsen T, McCord J, Huis In't Veld M, Massoomi M, Stopyra JP, Montero C, Weaver MT, Yang K and Mahler SA. Diagnostic Performance of High-Sensitivity Cardiac Troponin T Strategies and Clinical Variables in a Multisite US Cohort. *Circulation*. 2021;143:1659-1672.

18. Vigen R, Diercks DB, Hashim IA, Pandey A, Zhong L, Kutscher P, Fernandez F, Yu A, Bertulfo B, Molberg K, Metzger JC, Soto J, Alzubaidy D, Thibodeaux L, Joglar JA, Das SR and de Lemos JA. Association of a Novel Protocol for Rapid Exclusion of Myocardial Infarction With Resource Use in a US Safety Net Hospital. *JAMA Netw Open*. 2020;3:e203359.

19. Sandoval Y, Smith SW, Love SA, Sexter A, Schulz K and Apple FS. Single High-Sensitivity Cardiac Troponin I to Rule Out Acute Myocardial Infarction. *Am J Med*. 2017;130:1076-1083.e1.

20. Peacock WF, Baumann BM, Bruton D, Davis TE, Handy B, Jones CW, Hollander JE, Limkakeng AT, Mehrotra A, Than M, Ziegler A and Dinkel C. Efficacy of High-Sensitivity Troponin T in Identifying Very-Low-Risk Patients With Possible Acute Coronary Syndrome. *JAMA Cardiol*. 2018;3:104-111.

21. Ford JS, Chaco E, Tancredi DJ and Mumma BE. Impact of high-sensitivity cardiac troponin implementation on emergency department length of stay, testing, admissions, and diagnoses. *Am J Emerg Med*. 2021;45:54-60.

22. Mumma BE, Casey SD, Dang RK, Polen MK, Kaur JC, Rodrigo J, Tancredi DJ, Narverud RA, Amsterdam EA and Tran N. Diagnostic Reclassification by a High-Sensitivity Cardiac Troponin Assay. *Ann Emerg Med*. 2020;76:566-579.

23. Ganguli I, Cui J, Thakore N, Orav EJ, Januzzi JL, Baugh CW, Sequist TD and Wasfy JH. Downstream Cascades of Care Following High-Sensitivity Troponin Test Implementation. *J Am Coll Cardiol*. 2021;77:3171-3179.

24. Sandoval Y, Askew JW, 3rd, Newman JS, Clements CM, Grube ED, Ola O, Akula A, Dworak M, Wohlrab S, Karon BS and Jaffe AS. Implementing High-Sensitivity Cardiac Troponin T in a US Regional Healthcare System. *Circulation*. 2020;141:1937-1939.

25. AakreKM, SaengerAK, BodyR,CollinsonP,HammarstenO, JaffeAS, KavsakP, OmlandT, Ordonez-LianosJ, AppleFS. Analytical Considerations in Deriving 99th Percentile Upper Reference Limits for High-Sensitivity Cardiac Troponin Assays: Educational Recommendations from the IFCC Committee on Clinical Application of Cardiac Bio-Markers. Clinical Chemistry, in press.

26. Apple FS, Sandoval Y, Jaffe AS and Ordonez-Llanos J. Cardiac Troponin Assays: Guide to Understanding Analytical Characteristics and Their Impact on Clinical Care. *Clin Chem*. 2017;63:73-81.

27. Apple FS, Jaffe AS, Collinson P, Mockel M, Ordonez-Llanos J, Lindahl B, Hollander J, Plebani M, Than M and Chan MH. IFCC educational materials on selected analytical and clinical applications of high sensitivity cardiac troponin assays. *Clin Biochem*. 2015;48:201-3.

28. Januzzi JL, Jr., Mahler SA, Christenson RH, Rymer J, Newby LK, Body R, Morrow DA and Jaffe AS. Recommendations for Institutions Transitioning to High-Sensitivity Troponin Testing: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2019;73:1059-1077.

29. Tomaszewski CA, Nestler D, Shah KH, Sudhir A and Brown MD. Clinical Policy: Critical Issues in the Evaluation and Management of Emergency Department Patients With Suspected Non-ST-Elevation Acute Coronary Syndromes. *Ann Emerg Med*. 2018;72:e65-e106.

30. Musey PI, Jr., Bellolio F, Upadhye S, Chang AM, Diercks DB, Gottlieb M, Hess EP, Kontos MC, Mumma BE, Probst MA, Stahl JH, Stopyra JP, Kline JA and Carpenter CR. Guidelines for reasonable and appropriate care in the emergency department (GRACE): Recurrent, low-risk chest pain in the emergency department. *Acad Emerg Med*. 2021;28:718-744.

31. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW and Zieman SJ. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344-426.

32. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA and White HD. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation*. 2018;138:e618-e651.

33. Sandoval Y and Apple FS. The global need to define normality: the 99th percentile value of cardiac troponin. *Clin Chem*. 2014;60:455-62.

34. Sandoval Y, Apple FS, Saenger AK, Collinson PO, Wu AHB and Jaffe AS. 99th Percentile Upper-Reference Limit of Cardiac Troponin and the Diagnosis of Acute Myocardial Infarction. *Clin Chem*. 2020;66:1167-1180.

35. Apple FS, Wu AHB, Sandoval Y, Sexter A, Love SA, Myers G, Schulz K, Duh SH and Christenson RH. Sex-Specific 99th Percentile Upper Reference Limits for High Sensitivity Cardiac Troponin Assays Derived Using a Universal Sample Bank. *Clin Chem*. 2020;66:434-444.

36. Collinson PO, Heung YM, Gaze D, Boa F, Senior R, Christenson R and Apple FS. Influence of population selection on the 99th percentile reference value for cardiac troponin assays. *Clin Chem*. 2012;58:219-25.

37. Apple FS, Ler R and Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. *Clin Chem*. 2012;58:1574-81.

38. Wildi K, Gimenez MR, Twerenbold R, Reichlin T, Jaeger C, Heinzelmann A, Arnold C, Nelles B, Druey S, Haaf P, Hillinger P, Schaerli N, Kreutzinger P, Tanglay Y, Herrmann T, Moreno Weidmann Z, Krivoshei L, Freese M, Stelzig C, Puelacher C, Rentsch K, Osswald S and Mueller C. Misdiagnosis of Myocardial Infarction Related to Limitations of the Current Regulatory Approach to Define Clinical Decision Values for Cardiac Troponin. *Circulation*. 2015;131:2032-40.

39. Hachey BJ, Kontos MC, Newby LK, Christenson RH, Peacock WF, Brewer KC and McCord J. Trends in Use of Biomarker Protocols for the Evaluation of Possible Myocardial Infarction. *J Am Heart Assoc*. 2017;6.

40. Collinson P, Hammerer-Lercher A, Suvisaari J, Apple FS, Christenson RH, Pulkki K, van Dieijen-Visser MP, Duff CJ, Baum H, Stavljenic-Rukavina A, Aakre KM, Langlois MR, Stankovic S and Laitinen P. How Well Do Laboratories Adhere to Recommended Clinical Guidelines for the Management of Myocardial Infarction: The CARdiac MArker Guidelines Uptake in Europe Study (CARMAGUE). *Clin Chem*. 2016;62:1264-71.

41. Bagai A, Alexander KP, Berger JS, Senior R, Sajeev C, Pracon R, Mavromatis K, Lopez-Sendón JL, Gosselin G, Diaz A, Perna G, Drozdz J, Humen D, Petrauskiene B, Cheema AN, Phaneuf D, Banerjee S, Miller TD, Kedev S, Schuchlenz H, Stone GW, Goodman SG, Mahaffey KW, Jaffe AS, Rosenberg YD, Bangalore S, Newby LK, Maron DJ, Hochman JS and Chaitman BR. Use of troponin assay 99th percentile as the decision level for myocardial infarction diagnosis. *Am Heart J*. 2017;190:135-139.

42. Anand A, Shah ASV, Beshiri A, Jaffe AS and Mills NL. Global Adoption of High-Sensitivity Cardiac Troponins and the Universal Definition of Myocardial Infarction. *Clin Chem*. 2019;65:484-489.

43. Shah AS, Griffiths M, Lee KK, McAllister DA, Hunter AL, Ferry AV, Cruikshank A, Reid A, Stoddart M, Strachan F, Walker S, Collinson PO, Apple FS, Gray AJ, Fox KA, Newby DE and Mills NL. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *Bmj*. 2015;350:g7873.

44. Zhao Y, Izadnegahdar M, Lee MK, Kavsak PA, Singer J, Scheuermeyer F, Udell JA, Robinson S, Norris CM, Lyon AW, Pilote L, Cox J, Hassan A, Rychtera A, Johnson D, Mills NL, Christenson J and Humphries KH. High-Sensitivity Cardiac Troponin-Optimizing the Diagnosis of Acute Myocardial Infarction/Injury in Women (CODE-MI): Rationale and design for a multicenter, stepped-wedge, cluster-randomized trial. *Am Heart J*. 2020;229:18-28.

45. Chapman AR, Lee KK, McAllister DA, Cullen L, Greenslade JH, Parsonage W, Worster A, Kavsak PA, Blankenberg S, Neumann J, Sörensen NA, Westermann D, Buijs MM, Verdel GJE, Pickering JW, Than MP, Twerenbold R, Badertscher P, Sabti Z, Mueller C, Anand A, Adamson P, Strachan FE, Ferry A, Sandeman D, Gray A, Body R, Keevil B, Carlton E, Greaves K, Korley FK, Metkus TS, Sandoval Y, Apple FS, Newby DE, Shah ASV and Mills NL. Association of High-Sensitivity Cardiac Troponin I Concentration With Cardiac Outcomes in Patients With Suspected Acute Coronary Syndrome. *Jama*. 2017;318:1913-1924.

46. Chiang CH, Chiang CH, Pickering JW, Stoyanov KM, Chew DP, Neumann JT, Ojeda F, Sörensen NA, Su KY, Kavsak P, Worster A, Inoue K, Johannessen TR, Atar D, Amann M, Hochholzer W, Mokhtari A, Ekelund U, Twerenbold R, Mueller C, Bahrmann P, Buttinger N, Dooley M, Ruangsomboon O, Nowak RM, DeFilippi CR, Peacock WF, Neilan TG, Liu MA, Hsu WT, Lee GH, Tang PU, Ma KS, Westermann D, Blankenberg S, Giannitsis E, Than MP and Lee CC. Performance of the European Society of Cardiology 0/1-Hour, 0/2-Hour, and 0/3-Hour Algorithms for Rapid Triage of Acute Myocardial Infarction : An International Collaborative Meta-analysis. *Ann Intern Med*. 2022;175:101-113.

47. Pickering JW, Than MP, Cullen L, Aldous S, Ter Avest E, Body R, Carlton EW, Collinson P, Dupuy AM, Ekelund U, Eggers KM, Florkowski CM, Freund Y, George P, Goodacre S, Greenslade JH, Jaffe AS, Lord SJ, Mokhtari A, Mueller C, Munro A, Mustapha S, Parsonage W, Peacock WF, Pemberton C, Richards AM, Sanchis J, Staub LP, Troughton R, Twerenbold R, Wildi K and Young J. Rapid Rule-out of Acute Myocardial Infarction With a Single High-Sensitivity Cardiac Troponin T Measurement Below the Limit of Detection: A Collaborative Meta-analysis. *Ann Intern Med*. 2017;166:715-724.

48. Than MP, Aldous SJ, Troughton RW, Pemberton CJ, Richards AM, Frampton CMA, Florkowski CM, George PM, Bailey S, Young JM, Cullen L, Greenslade JH, Parsonage WA, Everett BM, Peacock WF, Jaffe AS and Pickering JW. Detectable High-Sensitivity Cardiac Troponin within the Population Reference Interval Conveys High 5-Year Cardiovascular Risk: An Observational Study. *Clin Chem*. 2018;64:1044-1053.

49. Sandoval Y, Smith SW and Apple FS. Present and Future of Cardiac Troponin in Clinical Practice: A Paradigm Shift to High-Sensitivity Assays. *Am J Med*. 2016;129:354-65.

50. Sandoval Y and Jaffe AS. Using High-Sensitivity Cardiac Troponin T for Acute Cardiac Care. *Am J Med*. 2017;130:1358-1365.e1.

51. Armbruster DA and Pry T. Limit of blank, limit of detection and limit of quantitation. *Clin Biochem Rev*. 2008;29 Suppl 1:S49-52.

52. Chapman AR, Sandeman D, Ferry AV, Stewart S, Strachan FE, Wereski R, Bularga A, Anand A, Shah ASV and Mills NL. Risk Stratification Using High-Sensitivity Cardiac Troponin T in Patients With Suspected Acute Coronary Syndrome. *J Am Coll Cardiol*. 2020;75:985-987.

53. Twerenbold R, Badertscher P, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Miró Ò, Martín-Sánchez FJ, Reichlin T and Mueller C. Effect of the FDA Regulatory Approach on the 0/1-h Algorithm for Rapid Diagnosis of MI. *J Am Coll Cardiol*. 2017;70:1532-1534.

54. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, Chapman AR, Langdon T, Sandeman D, Vaswani A, Strachan FE, Ferry A, Stirzaker AG, Reid A, Gray AJ, Collinson PO, McAllister DA, Apple FS, Newby DE and Mills NL. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet*. 2015;386:2481-8.

55. Chapman AR, Anand A, Boeddinghaus J, Ferry AV, Sandeman D, Adamson PD, Andrews J, Tan S, Cheng SF, D'Souza M, Orme K, Strachan FE, Nestelberger T, Twerenbold R, Badertscher P, Reichlin T, Gray A, Shah ASV, Mueller C, Newby DE and Mills NL. Comparison of the Efficacy and Safety of Early Rule-Out Pathways for Acute Myocardial Infarction. *Circulation*. 2017;135:1586-1596.

56. Sandoval Y, Lewis B, Mehta R, Ola O, Knott J, De Michieli L, Akula A, Lobo R, Yang E, Gharacholou S, Dworak M, Crockford E, Rastas N, Grube E, Karturi S, Wohlrab S, Hodge D, Tak T, Cagin C, Gulati R, and Jaffe AS. Rapid exclusion of acute myocardial injury and infarction with a single high sensitivity cardiac troponin T in the emergency department: a multicenter United States evaluation. Circulation, i<https://doi.org/10.1161/CIRCULATIONAHA.122.059235>Circulation. 2022;057.

57. Jaffe AS, Moeckel M, Giannitsis E, Huber K, Mair J, Mueller C, Plebani M, Thygesen K and Lindahl B. In search for the Holy Grail: suggestions for studies to define delta changes to diagnose or exclude acute myocardial infarction: a position paper from the study group on biomarkers of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care*. 2014;3:313-6.

58. Korley FK and Jaffe AS. Preparing the United States for high-sensitivity cardiac troponin assays. *J Am Coll Cardiol*. 2013;61:1753-8.

59. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, Wild P, Genth-Zotz S, Warnholtz A, Giannitsis E, Möckel M, Bickel C, Peetz D, Lackner K, Baldus S, Münzel T and Blankenberg S. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *Jama*. 2011;306:2684-93.

60. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, Meissner J, Haaf P, Potocki M, Drexler B, Osswald S and Mueller C. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation*. 2011;124:136-45.

61. Chapman AR, Adamson PD, Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Berry C, Findlay I, Cruikshank A, Reid A, Gray A, Collinson PO, Apple F, McAllister DA, Maguire D, Fox KAA, Vallejos CA, Keerie C, Weir CJ, Newby DE and Mills NL. High-Sensitivity Cardiac Troponin and the Universal Definition of Myocardial Infarction. *Circulation*. 2020;141:161-171.

62. Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, Giannitsis E, Gustafson S, Handy B, Katus H, Melanson SE, Panteghini M, Venge P, Zorn M, Jarolim P, Bruton D, Jarausch J and Jaffe AS. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clin Chim Acta*. 2011;412:748-54.

63. Donato LJ, Wockenfus AM, Katzman BM, Baumann NA, Jaffe AS and Karon BS. Analytical and Clinical Considerations in Implementing the Roche Elecsys Troponin T Gen 5 STAT Assay. *Am J Clin Pathol*. 2021;156:1121-1129.

64. Jaffe AS and White H. Ruling-In Myocardial Injury and Ruling-Out Myocardial Infarction With the European Society of Cardiology 1-Hour Algorithm. *Circulation*. 2016;134:1542-1545.

65. Reichlin T, Twerenbold R, Wildi K, Gimenez MR, Bergsma N, Haaf P, Druey S, Puelacher C, Moehring B, Freese M, Stelzig C, Krivoshei L, Hillinger P, Jäger C, Herrmann T, Kreutzinger P, Radosavac M, Weidmann ZM, Pershyna K, Honegger U, Wagener M, Vuillomenet T, Campodarve I, Bingisser R, Miró Ò, Rentsch K, Bassetti S, Osswald S and Mueller C. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. *Cmaj*. 2015;187:E243-e252.

66. Gunsolus I, Sandoval Y, Smith SW, Sexter A, Schulz K, Herzog CA and Apple FS. Renal Dysfunction Influences the Diagnostic and Prognostic Performance of High-Sensitivity Cardiac Troponin I. *J Am Soc Nephrol*. 2018;29:636-643.

67. Twerenbold R, Wildi K, Jaeger C, Gimenez MR, Reiter M, Reichlin T, Walukiewicz A, Gugala M, Krivoshei L, Marti N, Moreno Weidmann Z, Hillinger P, Puelacher C, Rentsch K, Honegger U, Schumacher C, Zurbriggen F, Freese M, Stelzig C, Campodarve I, Bassetti S, Osswald S and Mueller C. Optimal Cutoff Levels of More Sensitive Cardiac Troponin Assays for the Early Diagnosis of Myocardial Infarction in Patients With Renal Dysfunction. *Circulation*. 2015;131:2041-50.

68. Kadesjö E, Roos A, Siddiqui AJ, Sartipy U and Holzmann MJ. Causes of Death in Patients With Acute and Chronic Myocardial Injury. *Am J Med*. 2020;133:590-598.e2.

69. Bardají A, Bonet G, Carrasquer A, González-Del Hoyo M, Vásquez-Nuñez K, Ali S, Boqué C and Cediel G. Clinical Features and Prognosis of Patients with Acute and Chronic Myocardial Injury Admitted to the Emergency Department. *Am J Med*. 2019;132:614-621.

70. Melki D, Lugnegård J, Alfredsson J, Lind S, Eggers KM, Lindahl B and Jernberg T. Implications of Introducing High-Sensitivity Cardiac Troponin T Into Clinical Practice: Data From the SWEDEHEART Registry. *J Am Coll Cardiol*. 2015;65:1655-1664.

71. Hermann LK, Newman DH, Pleasant WA, Rojanasarntikul D, Lakoff D, Goldberg SA, Duvall WL and Henzlova MJ. Yield of routine provocative cardiac testing among patients in an emergency department-based chest pain unit. *JAMA Intern Med*. 2013;173:1128-33.

72. Reinhardt SW, Lin CJ, Novak E and Brown DL. Noninvasive Cardiac Testing vs Clinical Evaluation Alone in Acute Chest Pain: A Secondary Analysis of the ROMICAT-II Randomized Clinical Trial. *JAMA Intern Med*. 2018;178:212-219.

73. Foy AJ, Liu G, Davidson WR, Jr., Sciamanna C and Leslie DL. Comparative effectiveness of diagnostic testing strategies in emergency department patients with chest pain: an analysis of downstream testing, interventions, and outcomes. *JAMA Intern Med*. 2015;175:428-36.

74. Sandhu AT, Heidenreich PA, Bhattacharya J and Bundorf MK. Cardiovascular Testing and Clinical Outcomes in Emergency Department Patients With Chest Pain. *JAMA Intern Med*. 2017;177:1175-1182.

75. Sharp AL, Kawatkar AA, Baecker AS, Redberg RF, Lee MS, Ferencik M, Wu YL, Shen E, Zheng C, Park S, Goodacre S, Thokala P and Sun BC. Does Hospital Admission/Observation for Chest Pain Improve Patient Outcomes after Emergency Department Evaluation for Suspected Acute Coronary Syndrome? *J Gen Intern Med*. 2022;37:745-752.

76. Natsui S, Sun BC, Shen E, Redberg RF, Ferencik M, Lee MS, Musigdilok V, Wu YL, Zheng C, Kawatkar AA and Sharp AL. Higher Emergency Physician Chest Pain Hospitalization Rates Do Not Lead to Improved Patient Outcomes. *Circ Cardiovasc Qual Outcomes*. 2021;14:e006297.

77. Giannitsis E, Wallentin L, James SK, Bertilsson M, Siegbahn A, Storey RF, Husted S, Cannon CP, Armstrong PW, Steg PG and Katus HA. Outcomes after planned invasive or conservative treatment strategy in patients with non-ST-elevation acute coronary syndrome and a normal value of high sensitivity troponin at randomisation: A Platelet Inhibition and Patient Outcomes (PLATO) trial biomarker substudy. *Eur Heart J Acute Cardiovasc Care*. 2017;6:500-510.

78. Pickering JW, Greenslade JH, Cullen L, Flaws D, Parsonage W, George P, Worster A, Kavsak PA and Than MP. Validation of presentation and 3 h high-sensitivity troponin to rule-in and rule-out acute myocardial infarction. *Heart*. 2016;102:1270-8.

79. Chapman AR, Hesse K, Andrews J, Lee KK, Anand A, Shah ASV, Sandeman D, Ferry AV, Jameson J, Piya S, Stewart S, Marshall L, Strachan FE, Gray A, Newby DE and Mills NL. High-Sensitivity Cardiac Troponin I and Clinical Risk Scores in Patients With Suspected Acute Coronary Syndrome. *Circulation*. 2018;138:1654-1665.

80. Badertscher P, Boeddinghaus J, Twerenbold R, Nestelberger T, Wildi K, Wussler D, Schwarz J, Puelacher C, Rubini Giménez M, Kozhuharov N, du Fay de Lavallaz J, Cerminara SE, Potlukova E, Rentsch K, Miró Ò, López B, Martin-Sanchez FJ, Morawiec B, Muzyk P, Keller DI, Reichlin T and Mueller C. Direct Comparison of the 0/1h and 0/3h Algorithms for Early Rule-Out of Acute Myocardial Infarction. *Circulation*. 2018;137:2536-2538.

81. Sandoval Y, Smith SW, Schulz K, Sexter A and Apple FS. Comparison of 0/3-Hour Rapid Rule-Out Strategies Using High-Sensitivity Cardiac Troponin I in a US Emergency Department. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006565.

82. Than M, Herbert M, Flaws D, Cullen L, Hess E, Hollander JE, Diercks D, Ardagh MW, Kline JA, Munro Z and Jaffe A. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. *Int J Cardiol*. 2013;166:752-4.

83. Braunwald E and Morrow DA. Unstable angina: is it time for a requiem? *Circulation*. 2013;127:2452-7.

84. Sandoval Y, Apple FS and Smith SW. High-sensitivity cardiac troponin assays and unstable angina. *Eur Heart J Acute Cardiovasc Care*. 2018;7:120-128.

85. Puelacher C, Gugala M, Adamson PD, Shah A, Chapman AR, Anand A, Sabti Z, Boeddinghaus J, Nestelberger T, Twerenbold R, Wildi K, Badertscher P, Rubini Gimenez M, Shrestha S, Sazgary L, Mueller D, Schumacher L, Kozhuharov N, Flores D, du Fay de Lavallaz J, Miro O, Martín-Sánchez FJ, Morawiec B, Fahrni G, Osswald S, Reichlin T, Mills NL and Mueller C. Incidence and outcomes of unstable angina compared with non-ST-elevation myocardial infarction. *Heart*. 2019;105:1423-1431.

86.Heeschen C, Hamm CW, Goldmann B, et al.. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. **Lancet**. 1999; *354*:1757–62

87. Kastrati A, Mehilli J, Neumann FJ, et al.. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial.**JAMA**. 2006; *295*:1531–8.

88. Wiviott SD, Cannon CP, Morrow DA, Murphy SA, Gibson CM, McCabe CH, Sabatine MS, Rifai N, Giugliano RP, DiBattiste PM, Demopoulos LA, Antman EM, Braunwald E. Differential Expression of Cardiac Biomarkers by Gender in Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction A TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18) Substudy. Circulation 2004;109:580-586.

89.Sandoval Y and Jaffe AS. Type 2 Myocardial Infarction: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019;73:1846-1860.

90. DeFilippis AP, Chapman AR, Mills NL, de Lemos JA, Arbab-Zadeh A, Newby LK and Morrow DA. Assessment and Treatment of Patients With Type 2 Myocardial Infarction and Acute Nonischemic Myocardial Injury. *Circulation*. 2019;140:1661-1678.

**FIGURE LEGENDS**

**Figure 1.** Extensive data including observational studies, meta-analyses, and the largest hs-cTn randomized trial (Historic) showing that optimized rule out thresholds (for selected hs-cTn assay thus far) are a safe method to identify low risk patients.

**Figure 2.** Sex specific cut off values for hscTn assays

**Figure 3.** Threshold values for use with hs-cTn assays.

**Figure 4.**  Importance of changing patterns over time to distinguish acute from chronic myocardial injury. In addition, there is a balance between sensitivity and specificity for any given delta value. Adapted from data published in JAMA 2011;306:2684–93.

**Figure 5.**  Time concentration curve in patients with MI. Note the differences in the rapidly of the upslope compared to the downslope.

**Table 1.** European Society of Cardiology recommendations on hs-cTn assays.

|  |  |
| --- | --- |
| **ESC Guideline document** | **Recommendations** |
| 2011 ESC guidelines | * A rapid-rule out protocol (0 and 3 h) is recommend when highly sensitive troponin tests are available. Class IB. |
| 2015 ESC guidelines | * A rapid rule-out protocol at 0 h and 3 h is recommended if high sensitivity cardiac troponin tests are available. Class IB. * A rapid rule-out and rule-in protocol at 0 h and 1 h is recommended if a high-sensitivity cardiac troponin test with a validated 0 h/ 1h algorithm is available. Additional testing after 3-6 h is indicated if the first two troponin measurements are not conclusive and the clinical condition is still suggestive of ACS. Class IB. |
| 2020 ESC guidelines | * The ESC 0 h /1 h algorithm with blood sampling at 0 h and 1h is recommended if an hs-cTnT test with a validated 0 h/ 1 h algorithm is available. Class IB. * Additional testing after 3h is recommended if the first two cardiac troponin measurements of the 0 h/ 1h algorithm are not conclusive and the clinical conditions is still suggestive of ACS. Class IB. * As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs-cTn test with a validated 0 h/2 h algorithm is available. Class IB. * As an alternative to the ESC 0 h/1 h algorithm, a rapid rule-out and rule-in protocol with blood sampling at 0 h and 3 h should be considered, if a high sensitivity (or sensitive) cardiac troponin test with a validated 0 h/3 h algorithm is available. Class IIa-B. |

**Table 2**. ACEP and SAEM recommendations

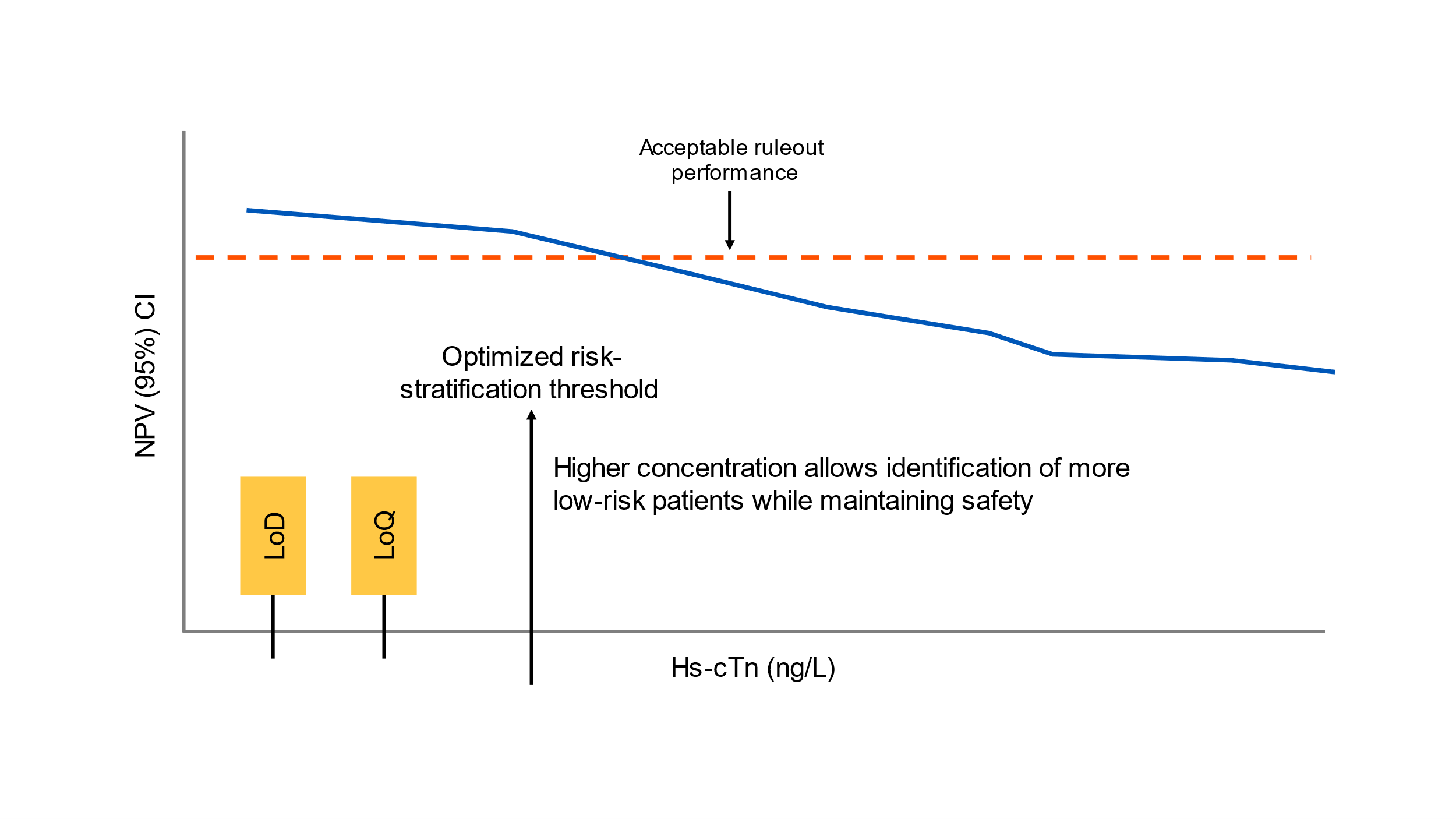
|  |  |
| --- | --- |
| **ACEP Clinical Policy (2018)** | **SAEM GRACE-1 guidelines (2021)** |
| In adult patients without evidence of ST-elevation ACS, the History, ECG, Age, Risk Factors, Troponin (HEART) score can be used as a clinical prediction instrument for risk stratification. A low score (<3) predicts 30-day MACE miss rate within a range of 0% to 2%. | In adult patients with recurrent, low-risk chest pain, for greater than 3h duration we suggest a single, high-sensitivity troponin below a validated threshold to reasonable exclude ACS within 30-days. |
| In adult patients without evidence of ST-elevation ACS, other risk-stratification tools, such as Thrombolysis in Myocardial Infarction (TIMI) can be used to predict rate of 30-day MACE. | In patients with recurrent, low-risk chest pain, and a normal stress test within the previous 12 months, we do not recommend repeat routine stress testing as a means to decrease rates of MACE at 30-days. |
| In adult patients with suspected acute NSTE-ACS, convention troponin testing at 0 and 3 hours among low-risk ACS (defined by HEART score 0 to 3) can predict an acceptable low rate of 30-day MACE. | In adult patients with recurrent, low-risk chest pain, there is insufficient evidence to recommend hospitalization (either standard inpatient admission or observation stay) versus discharge as a strategy to mitigate MACE within 30-days. |
| A single high-sensitivity troponin result below the level of detection on arrival to the ED, or negative serial high-sensitivity troponin result at 0 and 2 hours is predictive of a low rate of MACE. | In adult patients with recurrent, low-risk chest pain and non-obstructive (<50% stenosis) CAD on prior angiography within 5-years, we suggest referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. |
| In adult patients with suspected acute NSTE-ACS who are determined to be low risk based on validated ADPs that included a nonischemic ECG result and negative serial high-sensitivity troponin testing results both at presentation and at 2 hours can predict a low rate of 30-day MACE allowing for an accelerated discharge pathway from the ED. | In adult patients with recurrent, low-risk chest pain and no occlusive CAD (0% stenosis) on prior angiography within 5 years, we recommend referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. |
| Do not routinely use further diagnostic testing (coronary CT angiography, stress testing, myocardial perfusion imaging) prior to discharge in low-risk patients in whom acute MI has been ruled-out to reduce 30-day MACE. | In adult patients with recurrent, low-risk chest pain and prior CCTA within the past 2-years with no coronary stenoses, we suggest no further diagnostic testing other than a single, high-sensitivity troponin below a validated threshold to exclude ACS within that 2-year time frame. |
| Arrange follow-up in 1 to 2 weeks for low-risk patients in whom MI has been ruled out. If no follow-up is available, consider further testing or observation prior to discharge. | In adult patients with recurrent, low-risk chest pain, we suggest the use of depression and anxiety screening tools as these might have an effect on health care use and return ED visits. |
| P2Y12 inhibitors and glycoprotein IIb/IIIa inhibitors may be given in the ED or delayed until cardiac catheterization. | In adult patients with recurrent, low-risk chest pain, we suggest referral for anxiety or depression management, as this might have an impact on healthcare use and return ED visits. |

**Table 3.** FDA-cleared hs-cTn assays thresholds: LoD, LoQ, and 99th percentile upper-reference limits according to the insert package information. Source: reference 10.

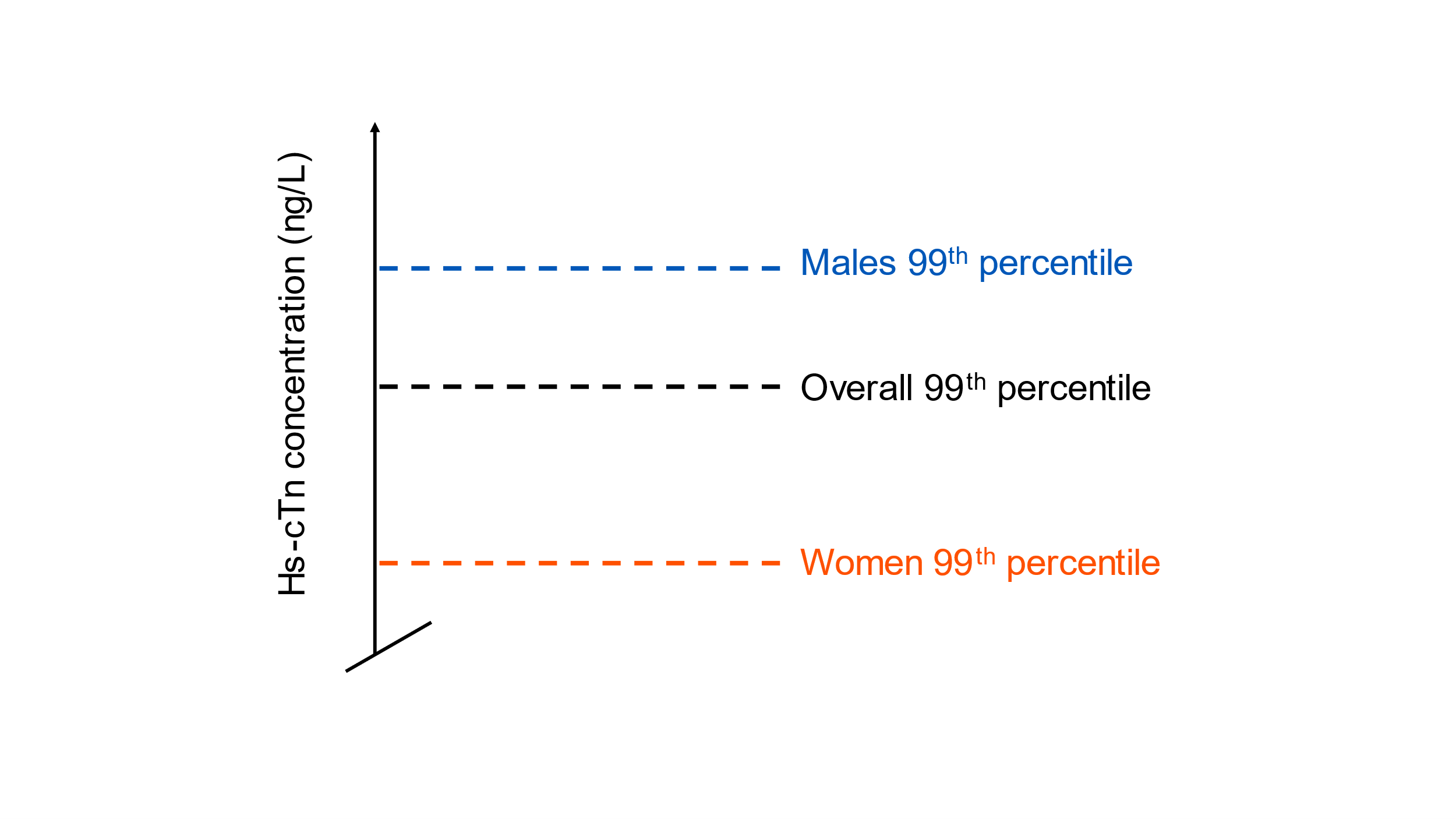
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Assay** | **LoD, ng/L** | **LoQ, ng/L** | **Overall 99th percentile, ng/L** | **Sex-specific 99th percentiles, ng/L** |
| Abbott ARCHITECT hs-cTnI | 1.7 | 2.3 | 28 | F 17, M 35 |
| Beckman Coulter / Access 2 hs-cTnI (plasma) | 1.0-2.0 | 0.9-2.3 | 17.5 | F 11.6, M 19.8 |
| Beckman Coulter / Access 2 hs-cTnI (serum) | 1.0-2.0 | 0.9-2.3 | 18.2 | F 11.8, M 19.7 |
| Beckman Coulter / DxI Access hs-cTnI (plasma) | 1.5-2.3 | 1.2-2.3 | 17.9 | F 14.9, M 19.8 |
| Beckman Coulter / DxI Access hs-cTnI (serum) | 1.5-2.3 | 1.2-2.3 | 18.1 | F 13.6, M 19.8 |
| Roche / cobas e601, e602, E170/ TnT Gen 5 STAT | 3; 5 for e411 | 6 | 19 | F 14, M 22 |
| Siemens ATELLICA High Sensitivity TnI (TNIH) | 1.6 | 2.50 | 45.4 | F 38.6, M 53.5 |
| Siemens ADVIA Centaur XP/XPT/CP High-Sensitivity TnI (TNIH) | 1.6 | 2.50 | 46.5 | F 39.6, M 58.0 |
| Siemens Dimension VISTA High Sensitivity TnI (TNIH) | 2.0 | 3.0 | 58.9 | F 53.7, M 78.5 |
| Siemens Dimension ExL High Sensitivity TnI (TNIH) | 2..7 | 4.0 | 60.4 | F 51.4, M 76.2 |

Beckman-Coulter has chosen to report their LOD as equal to the LoQ for ease of reporting.

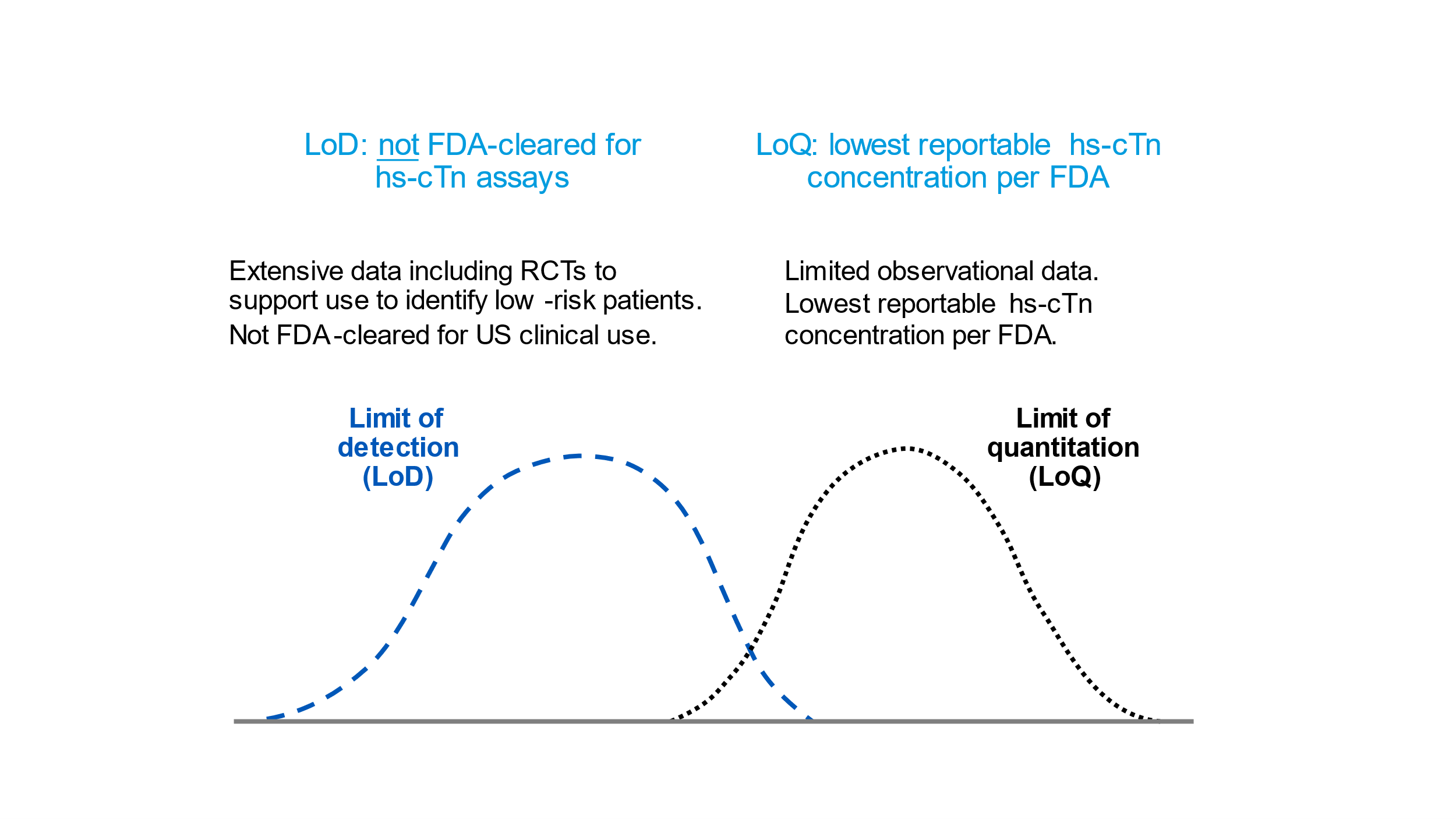
**Figure 1**



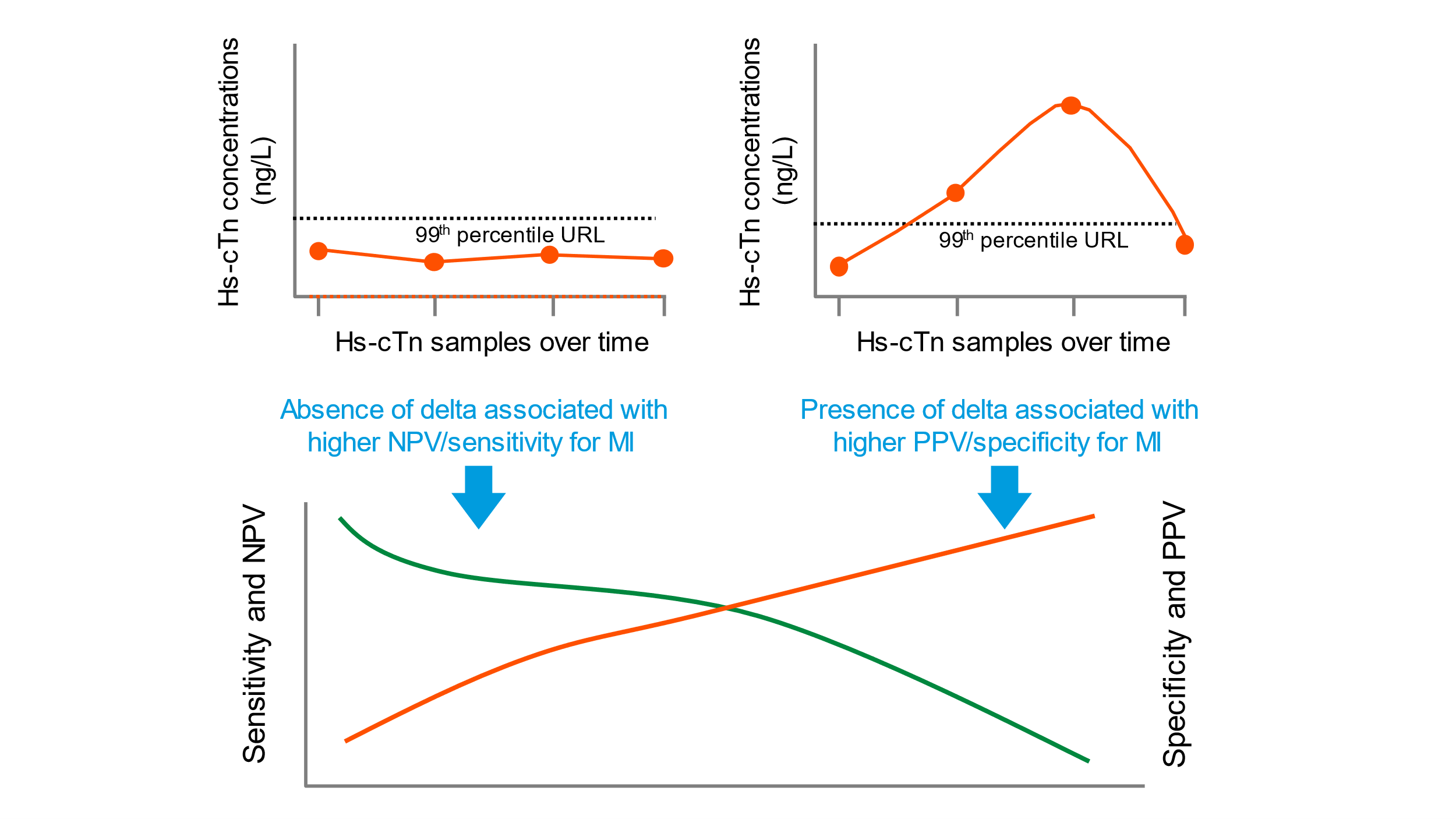
**Figure 2**



**Figure 3**



**Figure 4.** Time concentration curve in patients with MI. Reproduced with permission from reference 23. Note the differences in the rapidly of the upslope compared to the downslope.



**Figure 5**

